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MORGAN & FINNEGAN, L.L.P. 3 WORLD FINANCIAL CENTER NEW YORK, NY 10281-2101			EXAMINER BHAT, NARAYAN KAMESHWAR	
			ART UNIT 1634	PAPER NUMBER
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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<b>Office Action Summary</b>	<b>Application No.</b> 10/518,559	<b>Applicant(s)</b> OKAMOTO, TADASHI	
	<b>Examiner</b> Narayan K. Bhat	<b>Art Unit</b> 1634	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

**A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.**

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 09 November 2007.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-5, 8-29 and 32-38 is/are pending in the application.
- 4a) Of the above claim(s) 12, 16-23, 25, 26 and 36 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-5, 8-11, 13-15, 24, 27-29, 32-35 and 37-38 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

1. This office action is written in reply to applicant's correspondence filed November 9, 2007. Claims 1, 8, 10, 15, 24, 27, 32 and 34 were amended and claims 6-7 and 30-31 were cancelled.
2. Claims 1-5, 8-29, 32-38 are pending in this application.
3. Claims 12, 16-23, 25-26 and 36 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on June 18, 2007.
4. Claims 1-5, 8-11, 13-15, 24, 27-29, 32-35 and 37-38 are under prosecution.

### ***Amendments to Claims***

5. Amendments to the claims 1, 8, 10, 15, 24, 27, 32 and 34 have been reviewed and entered.

### ***Claim Rejections - 35 USC § 103***

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

7. Claims 1-5, 8-11, 13-15, 24, 27-29, 32-35 and 37-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over O'Donnell et al (WO 98/20020 published May 14, 1998) in view of Heckman et al (USPN 6,124,099 issued September 26, 2000) and further in view of Marriott et al (Biochemistry international, 1992, 26, 943-951, cited in the IDS of the instant invention).

Regarding claim 1, O'Donnell et al teaches a method of acquiring data on the mass of a substance fixed on a solid substrate (pg.7, lines 1-6), that includes immobilizing nucleic acids on the substrate using photo cleavable linker moiety (pg. 33, lines 12-17), thus teaching a structure including a partial structure to be disconnected by light to fix the substance on the substrate (pg. 33, 18-23); irradiating the substance fixed on the substrate with a laser (pg. 34, lines 26-28), which is light for inducing the disconnection of the partial structure to be disconnected by light; and analyzing the mass spectrum of the substance which is brought in an unfixed state by disconnecting the partial structure by the irradiation of light (Fig. 17, pg. 25 lines 7-29).

O'Donnell et al also teaches an exemplary photocleavable linker include 3-amino-(2-nitrophenyl) propionic acid (pg. 33, line 15, pgs. 38-47), which has the structure containing nitrobenzene and further teaches that the nitrobenzyl group as a photocleavable group (pg. 34, lines 3-9), thus teaching nitrobenzene is the selected partial structure to be disconnected by the irradiation of light.

O'Donnell et al do not teach the structure containing nitrobenzene is constructed with a compound represented by formula II, i.e., succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate (see instant specification paragraph 0115). However a

structure containing formula II, i.e., succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate was known in the art at the time of the claimed invention as taught by Heckman et al.

Heckman et al teaches a linker -succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate (column 3, lines 15-16). It is noted that the linker taught by Heckman et al is a photoactive cross linking agent, however, it is incorporated in to nucleic acid molecule (column 3, lines 19-29), which is a partial structure that responds to light, which meet the limitation of the claim. Heckman et al also teaches that the linker represented by formula II, attaches to the nucleic acid via covalent linkage and has very high long term stability in the dark (column 8, lines 21-27).

It would be obvious to one having the ordinary skill in the art at the time the invention was made to include the a linker -succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate of Heckman et al as an additional linker in the method of O'Donnell et al with the expected benefit of incorporating linker forming a covalent bond with a long term stability as taught by Heckman et al (column 8, lines 21-27).

O'Donnell et al in view of Heckman et al do not teach a photo cross-linking agent is also photocleavable. However light mediated chemical bond cleavage was known in the art at the time of the claimed invention was made as taught by Marriott et al who teaches 4-bromomethyl-3-nitrobenzoic acid succinimide ester to cross link F-actin, a biomolecule (Fig. 1a and b, pg. 944, paragraphs 3-6) and further teaches photocleavage of the cross linked biomolecules (pg. 944, paragraph 7). Marriott et al also teaches that light mediated chemical bond cleavage of nitrobenzyl derivative of biomolecules

provides a simple and effective method to generate concentration jumps of substrates and ligands in complex biological medium and further teaches the dissociation of the macromolecular complex through thioether linkage (Fig. 1b, Fig. 3a, pgs. 943, 944 and 948, paragraphs 1,1 and 1; pg. 948 lines 1-12).

It would be obvious to one having the ordinary skill in the art at the time the invention was made to modify the method of using Formula II linker of O'Donnell et al in view of Heckman et al and use the photocleavage of the photocross linked biomolecules of Marriott et al with the expected benefit of light mediated chemical bond cleavage of nitrobenzyl derivative of biomolecules, which provides a simple and effective method to generate concentration jumps of substrates and ligands in complex biological medium and to dissociate the macromolecular complex as taught by Marriott et al (Fig. 1b, Fig. 3a, pgs. 943, 944 and 948, paragraphs 1,1 and 1; pg. 948 lines 1-12), thus enhancing the utilities of the formula II linker in the method of acquiring data from mass of the substance.

Regarding claim 2, O'Donnell et al teaches a method that include a means of analyzing the mass spectrum is matrix assisted laser desorption ionization time-of-flight mass spectrometry (pg. 49, lines 17-22).

Regarding claim 3, O'Donnell et al teaches a laser, i.e., light for inducing the disconnection of the partial structure to be disconnected by light is a laser beam used for the analysis by MALDI-TOF MS (pg. 34, lines 26-28).

Regarding claim 4, O'Donnell et al teaches that the laser beam used for the analysis by MALDI-TOF MS is a nitrogen laser beam (pg. 73, line 7).

Regarding claim 5, O'Donnell et al teaches that the substance fixed on the substrate is nucleic acid (pg. 72, lines 20-22).

Regarding claim 8, O'Donnell et al teaches a substrate is a glass substrate (Fig. 7, Step1, pg. 49, lines 1-5) having a primary amino group formed on the surface (Fig. 7, step 2), a thiol (SH) group is bonded to the terminal of the nucleic acid substance, and the amino group and the thiol group are bonded together by a compound (Fig. 7, step 3). O'Donnell teaches different type of linkers including the SIAB linker and 3-amino-(2-nitrophenyl) propionic acid (pg. 33, line 15, pgs. 38-47) photocleavable linker to couple the nucleic acid substance to the substrate. Heckman et al teaches succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate (column 3, lines 15-16). Marriott et al teaches the BNBA-SE and nitrobenzyl group containing linker to crosslink actin molecules through amine and thio groups (Fig. 1a and b). The combined teachings of O'Donnell et al, Heckman et al and Marriott et al provides an embodiment which provides a reaction between the amino group and the succinimide ester site of the compound and a reaction between the thiol group and the bromobenzyl site of the compound.

Regarding claim 9, O'Donnell et al teaches the formation of a primary amino group on the glass substrate is carried out by using a silane coupling agent having the primary amino group (Fig. 7, pg. 23, lines 14-19).

Regarding claim 10, O'Donnell et al teaches a substrate is a glass substrate (pg. 49, lines 1-5) having a silane coupling agent having thiol group (pg. 65, lines 11-13) and further teaches sulfanil group formed on the surface by bonding of an amino group on

the terminal of the substance, and the thiol group on the substrate (pgs. 64 and 65, lines 24-29 and 1-27). Heckman et al teaches succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate (column 3, lines 15-16). Marriott et al teaches the BNBA-SE and nitrobenzyl group containing linker to crosslink actin molecules through amine and thio groups (Fig. 1a and b). The combined teachings of O'Donnell et al, Heckman et al and Marriott et al provides an embodiment which provides a reaction between the thiol group and the bromobenzyl site of the compound and a reaction between the amino group and the succinimide ester site of the compound.

Regarding claim 11, O'Donnell et al in view of Heckman et al teaches the formation of a thiol group on the glass substrate is carried out by using a silane coupling agent having the thiol group (pg. 65, lines 11-13).

Regarding claim 13, O'Donnell et al teaches a substance (matrix substance) for assisting the desorption and ionization of the substance fixed on the substrate is applied to at least a region to be used for the mass spectrometry of the substrate (pg. 81, lines 25-29).

Regarding claim 14, O'Donnell et al teaches the thickness of the coating film of the matrix substance is large enough and required for the desorption and ionization of the substance fixed on the substrate (Fig. 12, pg. 85, lines 20-29).

Regarding claim 15, O'Donnell et al a method of acquiring data on the mass of a nucleic acid, i.e., bio-related substance on each matrix of a biochip having a plurality of bio-related substances fixed on a substrate in a matrix form by a structure including a partial structure to be disconnected by light, the method comprising the steps of

immobilizing nucleic acids on the substrate in a matrix form (Fig. 14, pg. 24, lines 21-27), using photo cleavable linker moiety (pg. 33, lines 12-17) and further teaches irradiating the bio-related substance on each matrix fixed on the substrate with a laser (pg. 34, lines 26-28), which is light for inducing the disconnection of the partial structure to be disconnected by light; and analyzing the mass spectrum of the substance which is brought in an unfixed state by disconnecting the partial structure by the irradiation of light (Fig. 17, pg. 25 lines 7-29).

O'Donnell et al also teaches an exemplary photocleavable linker include 3-amino-(2-nitrophenyl) propionic acid (pg. 33, line 15, pgs. 38-47), which has the structure containing nitrobenzene and further teaches that the nitrobenzyl group as a photocleavable group (pg. 34, lines 3-9), thus teaching nitrobenzene is the selected partial structure to be disconnected by the irradiation of light.

O'Donnell et al do not teach the structure containing nitrobenzene is constructed with a compound represented by formula II, i.e., succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate (see instant specification paragraph 0115). However a structure containing formula II, i.e., succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate was known in the art at the time of the claimed invention as taught by Heckman et al.

Heckman et al teaches a linker -succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate (column 3, lines 15-16). It is noted that the linker taught by Heckman et al is a photoactive cross linking agent, however, it is incorporated in to nucleic acid molecule (column 3, lines 19-29), which is a partial structure that responds to light,

which meet the limitation of the claim. Heckman et al also teaches that the linker represented by formula II, attaches to the nucleic acid via covalent linkage and has very high long term stability in the dark (column 8, lines 21-27).

It would be obvious to one having the ordinary skill in the art at the time the invention was made to include the a linker -succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate of Heckman et al as an additional linker in the method of O'Donnell et al with the expected benefit of incorporating linker forming a covalent bond with a long term stability as taught by Heckman et al (column 8, lines 21-27).

O'Donnell et al in view of Heckman et al do not teach a photo cross-linking agent is also photocleavable. However light mediated chemical bond cleavage was known in the art at the time of the claimed invention was made as taught by Marriott et al who teaches 4-bromomethyl-3-nitrobenzoic acid succinimide ester to cross link F-actin, a biomolecule (Fig. 1a and b, pg. 944, paragraphs 3-6) and further teaches photocleavage of the cross linked biomolecules (pg. 944, paragraph 7). Marriott et al also teaches that light mediated chemical bond cleavage of nitrobenzyl derivative of biomolecules provides a simple and effective method to generate concentration jumps of substrates and ligands in complex biological medium and further teaches the dissociation of the macromolecular complex through thioether linkage (Fig. 1b, Fig. 3a, pgs. 943, 944 and 948, paragraphs 1,1 and 1; pg. 948 lines 1-12).

It would be obvious to one having the ordinary skill in the art at the time the invention was made to modify the method of using Formula II linker of O'Donnell et al in view of Heckman et al and use the photocleavage of the photocross linked

biomolecules of Marriott et al with the expected benefit of light mediated chemical bond cleavage of nitrobenzyl derivative of biomolecules, which provides a simple and effective method to generate concentration jumps of substrates and ligands in complex biological medium and to dissociate the macromolecular complex as taught by Marriott et al (Fig. 1b, Fig. 3a, pgs. 943, 944 and 948, paragraphs 1,1 and 1; pg. 948 lines 1-12), thus enhancing the utilities of the formula II linker in the method of acquiring data from mass of the substance.

Regarding claim 24, O'Donnell et al teaches method of acquiring data on the mass of a nucleic acid, i.e., a bio-related substance on each matrix of a biochip having a plurality of bio-related substances fixed on a substrate in a matrix form and the mass of a substance which interacts with the bio-related substance, the method comprising the steps of: fixing the bio-related substance on each matrix on the substrate (Fig. 14, pg. 24, lines 21-27) by photo cleavable linker (pg. 33, lines 12-17), that is a structure including a partial structure to be disconnected by light; placing the substance which interacts with the bio-related substance on each matrix of the biochip under an interactive condition (pg. 81, lines 25-29; See the entire sample preparation and dispensing section); irradiating the bio-related substance fixed on the substrate with a laser (pg. 34, lines 26-28), that is a light for inducing the disconnection of the partial structure to be disconnected by light; and analyzing the mass spectra of the bio-related substance which has been brought in an unfixed state by the irradiation of light and the substance which has interacted with the bio-related substance in an unfixed state at the

same time by disconnecting the partial structure (Figs. 16-18, pg. 25, lines 7-29; Example 5).

O'Donnell et al also teaches an exemplary photocleavable linker include 3-amino-(2-nitrophenyl) propionic acid (pg. 33, line 15, pgs. 38-47), which has the structure containing nitrobenzene and further teaches that the nitrobenzyl group as a photocleavable group (pg. 34, lines 3-9), thus teaching nitrobenzene is the selected partial structure to be disconnected by the irradiation of light.

O'Donnell et al do not teach the structure containing nitrobenzene is constructed with a compound represented by formula II, i.e., succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate (see instant specification paragraph 0115). However a structure containing formula II, i.e., succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate was known in the art at the time of the claimed invention as taught by Heckman et al.

Heckman et al teaches a linker -succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate (column 3, lines 15-16). It is noted that the linker taught by Heckman et al is a photoactive cross linking agent, however, it is incorporated in to nucleic acid molecule (column 3, lines 19-29), which is a partial structure that responds to light, which meet the limitation of the claim. Heckman et al also teaches that the linker represented by formula II, attaches to the nucleic acid via covalent linkage and has very high long term stability in the dark (column 8, lines 21-27).

It would be obvious to one having the ordinary skill in the art at the time the invention was made to include the a linker -succinimidyl 6-(4-bromomethyl-3-

nitrobenzoyl) aminohexanoate of Heckman et al as an additional linker in the method of O'Donnell et al with the expected benefit of incorporating linker forming a covalent bond with a long term stability as taught by Heckman et al (column 8, lines 21-27).

O'Donnell et al in view of Heckman et al do not teach a photo cross-linking agent is also photocleavable. However light mediated chemical bond cleavage was known in the art at the time of the claimed invention was made as taught by Marriott et al who teaches 4-bromomethyl-3-nitrobenzoic acid succinimide ester to cross link F-actin, a biomolecule (Fig. 1a and b, pg. 944, paragraphs 3-6) and further teaches photocleavage of the cross linked biomolecules (pg. 944, paragraph 7). Marriott et al also teaches that light mediated chemical bond cleavage of nitrobenzyl derivative of biomolecules provides a simple and effective method to generate concentration jumps of substrates and ligands in complex biological medium and further teaches the dissociation of the macromolecular complex through thioether linkage (Fig. 1b, Fig. 3a, pgs. 943, 944 and 948, paragraphs 1,1 and 1; pg. 948 lines 1-12).

It would be obvious to one having the ordinary skill in the art at the time the invention was made to modify the method of using Formula II linker of O'Donnell et al in view of Heckman et al and use the photocleavage of the photocross linked biomolecules of Marriott et al with the expected benefit of light mediated chemical bond cleavage of nitrobenzyl derivative of biomolecules, which provides a simple and effective method to generate concentration jumps of substrates and ligands in complex biological medium and to dissociate the macromolecular complex as taught by Marriott et al (Fig. 1b, Fig. 3a, pgs. 943, 944 and 948, paragraphs 1,1 and 1; pg. 948 lines 1-12),

thus enhancing the utilities of the formula II linker in the method of acquiring data from mass of the substance.

Regarding claim 27, O'Donnell et al teaches a method of determining a base sequence of nucleic acid, comprising the steps of: (1) fixing, to a substrate, nucleic acid (DNA) complementary to a part or an entire part of a base sequence on a 3'-side from a site desired for analysis of a base sequence of nucleic acid (DNA) desired for analysis of the base sequence as a primer used for performing an enzymatic nucleic acid extension reaction, using the nucleic acid desired for analysis of the base sequence as a template, in a structure containing a partial structure to be disconnected by light on a 5'-side from the complimentary base sequence in the primer (Figs. 18 and 19, pg. 25 and 26, lines 24-29 and 1-22); (2) annealing the nucleic acid desired for analysis of the base sequence to the primer fixed to the substrate at the complementary base sequence portion to form a hybrid (Fig. 18, top left panel) ; (3) performing the enzymatic extension reaction using the nucleic acid desired for analysis of the base sequence as a template, on the substrate where the hybrid is formed, in the presence of appropriate amounts of 4 kinds of 2'-deoxynucleotide triphosphate (dNTP: N is A; adenine, G; guanine, C; cytosine, T; thymine) required for the enzymatic nucleic acid extension reaction and the 4 kinds of 2',3'-dideoxynucleotide triphosphate (ddNTP) as a terminator for an extension reaction (Fig. 18, Top left panel, see the step probe with ddT, pg. 26, lines 1-8 )

O'Donnell et al also teaches removing the template nucleic acid from the substrate where the extension reaction is effected (pg. 37, lines 1-20, step 4 of the said

claim) and further teaches irradiating a plurality of extension reaction products having different chain lengths including a primer portion fixed to the substrate (Fig. 19).

O'Donnell et al also teaches photo cleavable linker moiety (pg. 33, lines 12-17) that is a structure containing a partial structure to be disconnected by a laser (pg. 34, lines 26-28), that is light, for disconnecting the partial structure to be disconnected, analyzing a molecular weight of the extension product disconnected by the irradiation with light by a MALDI-TOF MS method, and clarifying a base sequence of an extension portion of the extension product based on an increase in a molecular weight from a molecular weight of the primer in the extension product (Fig. 20, pg. 26, lines 24-29, step 5 of the said claim ; and (6) analyzing a part or an entire part of the base sequence desired for analysis of nucleic acid desired for analysis of the base sequence, based on the base sequence of the extension portion (Example 6 and 7, pg. 91-93) .

O'Donnell et al also teaches an exemplary photocleavable linker include 3-amino-(2-nitrophenyl) propionic acid (pg. 33, line 15, pgs. 38-47), which has the structure containing nitrobenzene and further teaches that the nitrobenzyl group as a photocleavable group (pg. 34, lines 3-9), thus teaching nitrobenzene is the selected partial structure to be disconnected by the irradiation of light.

O'Donnell et al do not teach the structure containing nitrobenzene is constructed with a compound represented by formula II, i.e., succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate (see instant specification paragraph 0115). However a structure containing formula II, i.e., succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl)

aminohexanoate was known in the art at the time of the claimed invention as taught by Heckman et al.

Heckman et al teaches a linker -succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate (column 3, lines 15-16). It is noted that the linker taught by Heckman et al is a photoactive cross linking agent, however, it is incorporated in to nucleic acid molecule (column 3, lines 19-29), which is a partial structure that responds to light, which meet the limitation of the claim. Heckman et al also teaches that the linker represented by formula II, attaches to the nucleic acid via covalent linkage and has very high long term stability in the dark (column 8, lines 21-27).

It would be obvious to one having the ordinary skill in the art at the time the invention was made to include the a linker -succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate of Heckman et al as an additional linker in the method of O'Donnell et al with the expected benefit of incorporating linker forming a covalent bond with a long term stability as taught by Heckman et al (column 8, lines 21-27).

O'Donnell et al in view of Heckman et al do not teach a photo cross-linking agent is also photocleavable. However light mediated chemical bond cleavage was known in the art at the time of the claimed invention was made as taught by Marriott et al who teaches 4-bromomethyl-3-nitrobenzoic acid succinimide ester to cross link F-actin, a biomolecule (Fig. 1a and b, pg. 944, paragraphs 3-6) and further teaches photocleavage of the cross linked biomolecules (pg. 944, paragraph 7). Marriott et al also teaches that light mediated chemical bond cleavage of nitrobenzyl derivative of biomolecules provides a simple and effective method to generate concentration jumps of substrates

and ligands in complex biological medium and further teaches the dissociation of the macromolecular complex through thioether linkage (Fig. 1b, Fig. 3a, pgs. 943, 944 and 948, paragraphs 1,1 and 1; pg. 948 lines 1-12).

It would be obvious to one having the ordinary skill in the art at the time the invention was made to modify the method of using Formula II linker of O'Donnell et al in view of Heckman et al and use the photocleavage of the photocross linked biomolecules of Marriott et al with the expected benefit of light mediated chemical bond cleavage of nitrobenzyl derivative of biomolecules, which provides a simple and effective method to generate concentration jumps of substrates and ligands in complex biological medium and to dissociate the macromolecular complex as taught by Marriott et al (Fig. 1b, Fig. 3a, pgs. 943, 944 and 948, paragraphs 1,1 and 1; pg. 948 lines 1-12), thus enhancing the utilities of the formula II linker in the method of acquiring data from mass of the substance.

Regarding claim 28, O'Donnell et al teaches a laser, i.e., light for inducing the disconnection of the partial structure to be disconnected by light is a laser beam used for the analysis by MALDI-TOF MS (pg. 34, lines 26-28),

Regarding claim 29, O'Donnell et al teaches that the laser beam used for the analysis by MALDI-TOF MS is a nitrogen laser beam (pg. 73, line 7).

Regarding claim 32, O'Donnell et al teaches a substrate is a glass substrate (pg. 49, lines 1-5) having a silane coupling agent having thiol group (pg. 65, lines 11-13) and further teaches sulfanyl group formed on the surface by bonding of an amino group on the terminal of the substance, and the thiol group on the substrate (pgs. 64 and 65, lines

24-29 and 1-27). Heckman et al teaches succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate (column 3, lines 15-16). Marriott et al teaches the BNBA-SE and nitrobenzyl group containing linker to crosslink actin molecules through amine and thio groups (Fig. 1a and b). The combined teachings of O'Donnell et al, Heckman et al and Marriott et al provides an embodiment which provides a reaction between the thiol group and the bromobenzyl site of the compound and a reaction between the amino group and the succinimide ester site of the compound.

Regarding claim 33, O'Donnell et al in view of Heckman et al teaches the formation of a primary amino group on the glass substrate is carried out by using a silane coupling agent having the primary amino group (Fig. 7, pg. 23, lines 14-19).

Regarding claim 34, O'Donnell et al teaches a substrate is a glass substrate (pg. 49, lines 1-5) having a silane coupling agent having thiol group (pg. 65, lines 11-13) and further teaches sulfanyl group formed on the surface by bonding of an amino group on the terminal of the substance, and the thiol group on the substrate (pgs. 64 and 65, lines 24-29 and 1-27). Heckman et al teaches succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate (column 3, lines 15-16). Marriott et al teaches the BNBA-SE and nitrobenzyl group containing linker to crosslink actin molecules through amine and thio groups (Fig. 1a and b). The combined teachings of O'Donnell et al, Heckman et al and Marriott et al provides an embodiment which provides a reaction between the thiol group and the bromobenzyl site of the compound and a reaction between the amino group and the succinimide ester site of the compound.

Regarding claim 35, O'Donnell et al in view of Heckman et al teaches that a sulfanil group is formed on the glass substrate by using a silane coupling agent having a sulfanil group (Fig. 7, last step, pg. 65, lines 5-27). Heckman et al teaches succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate (column 3, lines 15-16). Marriott et al teaches the BNBA-SE and nitrobenzyl group containing linker to crosslink actin molecules through amine and thio groups (Fig. 1a and b). The combined teachings of O'Donnell et al, Heckman et al and Marriott et al provides an embodiment which provides a sulfanil group formed on the glass substrate by using a silane coupling agent having a sulfanil group.

Regarding claim 37, O'Donnell et al teaches a Thermo sequenase, an enzyme used for the extension reaction has heat resisting property (Fig. 19, pg. 92, lines 1-3).

Regarding claim 38, O'Donnell et al teaches a method wherein the substrate to which the primer is fixed is in a form of a nucleic acid chip in which a plurality of primer nucleic acids are placed in a matrix in the process (Fig. 19, pg. 83, lines 1-15) a part or an entire part of the primer nucleic acid is subjected to an enzymatic nucleic acid extension reaction together with the template thereof on the nucleic acid chip, and in the process (4), the matrix portion subjected to the extension reaction is analyzed by the MALDI-TOF MS method (pg. 83, lines 16-24).

***Response to Remarks from the applicants***

***Rejections under 35 U.S.C. § 102(b)***

8. Applicant's arguments with respect to claims 1-6, 13-15, 24, 27-30 and 37-38 as being anticipated by O'Donnell et al have been fully considered but are moot in view of the new grounds of rejection.

***Rejections under 35 U.S.C. § 103(a)***

9. Applicant's arguments with respect to claims 1, 6-11, 27 and 31-35 as being unpatentable over O'Donnell et al have been fully considered but are moot in view of the new grounds of rejection necessitated by Applicant's amendment to claims.

As described in this office action in detail, claims 1-5, 8-11, 13-15, 24, 27-29, 32-35 and 37-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over O'Donnell et al (WO 98/20020 published May 14, 1998) in view of Heckman et al (USPN 6,124,099 issued September 26, 2000) and further in view of Marriott et al (Biochemistry international, 1992, 26, 943-951, cited in the IDS of the instant invention).

O'Donnell et al teaches all the steps recited in independent claims 1, 15, 24 and 27 and dependent claims except for the linker or compound represented by formula II of the instant claim, which Heckman et al teaches (column 3, lines 15-16). It is noted that the linker taught by Heckman et al is a photoactive cross linking agent, which is incorporated in to nucleic acid molecule (Heckman et al, column 3, lines 19-29) generating a structure that responds to light. As described in this office action, Heckman

et al provides a motivation for using the compound to attach the nucleic acid via covalent linkage and such nucleic acid structure has very high long term stability in the dark (Heckman et al column 8, lines 21-27).

The teachings of O'Donnell et al in view of Heckman et al do not teach a photo cross-linking agent is also photocleavable, which is taught by Marriott et al who teaches 4-bromomethyl-3-nitrobenzoic acid succinimide ester to cross link F-actin, a biomolecule (Fig. 1a and b, pg. 944, paragraphs 3-6) and further teaches photocleavage of the cross linked biomolecules (pg. 944, paragraph 7). Marriott et al also teaches that light mediated chemical bond cleavage of nitrobenzyl derivative of biomolecules provides a simple and effective method to generate concentration jumps of substrates and ligands in complex biological medium and further teaches the dissociation of the macromolecular complex through thioether linkage (Fig. 1b, Fig. 3a, pgs. 943, 944 and 948, paragraphs 1, 1 and 1; pg. 948 lines 1-12). The teachings of Marriott et al provides a motivation for one of the ordinary skill in the art to use formula II to construct a photocleavable structure based on the teachings of O'Donnell et al and Heckman et al to use the photocleavage of the photocross linked biomolecules of Marriott et al with the expected benefit of light mediated chemical bond cleavage of nitrobenzyl derivative of biomolecules, which provides a simple and effective method to generate concentration jumps of substrates and ligands in complex biological medium and to dissociate the macromolecular complex as taught by Marriott et al (Fig. 1b, Fig. 3a, pgs. 943, 944 and 948, paragraphs 1, 1 and 1; pg. 948 lines 1-12), thus enhancing the utilities of the formula II linker in the method of acquiring data from mass of the substance. Therefore

Applicant's argument of "one of ordinary skill in the art would not be motivated to use formula II to construct a photocleavable structure based on the teachings of O'Donnell et al or Heckman et al nor would one have a reasonable expectation of success" is not persuasive.

### ***Conclusion***

10. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Narayan K. Bhat whose telephone number is (571)-272-5540. The examiner can normally be reached on 8.30 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram R. Shukla can be reached on (571)-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Narayan K. Bhat, Ph. D.

Examiner

Art Unit 1634



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PRIMARY EXAMINER